Racial differences in microbleed prevalence in primary intracerebral hemorrhage

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ABSTRACT

Background: Primary intracerebral hemorrhage is two to three times more common in many racial populations, including black patients. Previous studies have shown that microbleeds, identified on gradient echo MRI (GRE), are present in 50–80% of patients with primary ICH. The objective of this study was to compare, by race, the rates, risk factors, and topography of microbleeds in patients hospitalized for primary ICH.

Methods: Patients diagnosed with primary ICH at two metropolitan stroke centers were included. Clinical and neuroimaging data were recorded for each patient. Analyses were performed to compare baseline characteristics as well as imaging findings by race.

Results: A total of 87 patients met inclusion criteria (42 black subjects, 45 white subjects). The black cohort was younger ($p < 0.001$), and had a greater rate of hypertension ($p = 0.001$), but not other vascular risk factors. Microbleeds were more prevalent in the black population, with 74% of blacks having one or more microbleeds compared to 42% of whites ($p = 0.005$). The black population also tended to have a greater frequency of microbleeds in multiple territories than the white population (38% vs 22%, $p = 0.106$). When adjusting for age, hypertension, and alcohol use, race was an independent predictor of microbleeds (OR 3.308, 95% CI 1.144–9.571, $p = 0.027$).

Conclusions: These pilot data suggest that significant racial differences exist in the frequency and topography of microbleeds in patients with primary ICH. Microbleeds may be an important emerging imaging biomarker with the potential to provide insights into ICH pathophysiology, prognosis, and disease progression, as well as possible therapeutic strategies, particularly in medically underserved populations. ***Neurology*® 2008;71:1176–1182**

GLOSSARY

CAA = cerebral amyloid angiopathy; **FLAIR** = fluid-attenuated inversion recovery; **FOV** = field of view; **GRE** = gradient echo imaging; **SES** = socioeconomic status; **TE** = echo time; **TR** = repetition time.

Intracerebral hemorrhage is a devastating disease with poor prognosis and high mortality rates ranging from 25 to 50%.[1] Hemorrhage is the underlying etiology in 10–15% of all strokes with 75% of those being attributed to primary (nontraumatic) intraparenchymal hemorrhage.

The most frequent vascular risk factors associated with primary ICH are hypertension and cerebral amyloid angiopathy (CAA), with the likely underlying pathophysiology varying by hemorrhage location.[2] Primary ICH associated with hypertension most often occurs in deep brain structures and is generally attributed to rupture of small penetrating arteries damaged by hypertension. In contrast, primary ICH associated with CAA most often occurs in lobar regions and is generally attributed to vasculopathic changes that occur in amyloid-laden vessels.[3]

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Chronic cerebral microbleeds visualized on magnetic resonance gradient echo imaging (GRE) have emerged as an important imaging marker of these bleeding-prone microangiopathies. Pathologic studies have demonstrated that GRE-visualized microbleeds usually represent hemosiderin-laden macrophages that occur adjacent to small vessels and are indicative of previous extravasation of blood.[4] Microbleeds are present in 50–80% of patients with primary ICH and the topography of microbleeds has traditionally been reported to track that of the primary ICH.[5-13] Thus patients with CAA tend to have lobar microbleeds and lobar hemorrhages, whereas patients with hypertensive disease tend to have deep microbleeds and deep hemorrhages.[11,14]

Few studies have compared the prevalence of microbleeds by race or ethnicity. The goal of this pilot study was to examine the incidence of microbleeds in a population of white and black patients presenting with primary ICH and to explore the association between race and microbleeds and their underlying risk factors.

METHODS We performed a retrospective chart review of patients admitted to two metropolitan hospitals staffed by the same stroke team: Suburban Hospital, Bethesda, MD, and Washington Hospital Center, Washington, DC. Patients were identified through a stroke registry/database. Data were available from Suburban Hospital from 2000 to 2007, and from Washington Hospital Center from 2004 to 2007. Suburban Hospital serves a predominantly middle class white population, while Washington Hospital Center serves a predominantly lower middle class black population that has been officially designated as medically underserved. All potential patients with stroke at both hospitals underwent routine MRI studies including a GRE sequence, unless a contraindication to MRI existed. The study was performed in accordance with the Institutional Review Boards of both hospitals.

Patients were included in the study if 1) their diagnosis was primary intracerebral hemorrhage (not limited to first ICH), 2) an MRI with GRE and fluid-attenuated inversion recovery (FLAIR) sequences was performed within 1 month of their admission for primary ICH, and 3) their race was specified as black or white. There were insufficient numbers of other races/ethnicities to provide a meaningful analysis. A diagnosis of primary (nontraumatic) ICH was given after each patient underwent routine imaging and diagnostic evaluations to identify an underlying cause for the hemorrhage including MRI in all patients, and typically cerebral angiography for patients with unexplained lobar hemorrhages or absence of vascular risk factors.

The following clinical information was extracted from the medical record of each patient: age, sex, risk factors for ICH (prior stroke, hypertension, coronary artery disease [CAD], diabetes mellitus, hyperlipidemia, tobacco use), medications at time of admission, heavy alcohol use (>2 drinks/day), and active treatment with antiplatelet or anticoagulant therapy at the time of admission. Race (using US Census Bureau classifications) was assigned by a physician incorporating information provided by the medical record and confirmed with the subject. Vascular risk factors were identified by prior history at the time of admission. Hypertension was defined by prior medical history. Untreated hypertension was defined as absence of antihypertensive medication at the time of admission in any patient with a history of hypertension. There was insufficient information in the medical record to extract information about socioeconomic status (SES).

Images were acquired using a gradient recalled echo sequence at Suburban Hospital on a 1.5 T (General Electric) scanner and at Washington Hospital Center on a 3.0 T (Philips) scanner. For the 1.5 T system: repetition time (TR)/echo time (TE) 800/20 msec, field of view (FOV) = 24 cm, 256 × 192 matrix, 20 7-mm-thick contiguous but interleaved axial-oblique slices aligned with the AC-PC, 30° flip angle, NEX = 1, SENSE = 1. For the 3.0 T system: TR/TE 875/11 msec, FOV = 22.4 cm, 224 × 112 matrix, 35 4-mm-thick contiguous but interleaved axial-oblique slices aligned with the AC-PC, 40° flip angle, NEX = 1/2, SENSE = 2.

A related but separate study was performed to ensure that differences in magnet strength did not impact the number of microbleeds detected.[15] For this secondary study 31 patients (independent from the patients included in the current study) underwent scanning with gradient echo imaging on both a 1.5 T and 3.0 T scanner a median of 3 days apart (range 0–280). The scan parameters (TR/TE/slice thickness) for the 1.5 T and 3.0 T systems were the same as those employed for the current 87-subject study. Scans were independently interpreted by an experienced stroke neurologist and a neuroradiologist blinded to field strength and patient identity. There was no difference between the number of microbleeds detected on 1.5 T ($p \leq 0.8$) compared to 3.0 T MRI ($p \leq 0.9$) for the two readers. A total of 35% of scans were microbleed positive on the 1.5 T vs 32% on the 3.0 T. There were 10 cases in which there was a discrepancy in number of microbleeds between field strengths (range of discrepancies 1–4). In half of these cases, more microbleeds were seen on the 1.5 T scans. Inter-rater agreement for the presence of microbleeds yielded a kappa of 0.86.

One investigator (C.K.) interpreted the imaging data for the current analysis blinded to clinical information. The following data points were assessed employing the gradient echo sequences: ICH location (lobar, subcortical/deep, infratentorial), total number of microbleeds, number of microbleeds by location (lobar, subcortical/deep, infratentorial), and total number of chronic hematomas. Microbleeds were defined as rounded, punctate, homogenous hypointensities generally <5–10 mm in size located within the parenchyma. Hypointensities appearing in sulci consistent with vessels visualized end-on were not counted as microbleeds. Symmetric hypointensities in the basal ganglia most likely represent calcifications or iron deposition and were not counted as microbleeds. Chronic hematomas were defined as slit like regions of hypointensity. FLAIR sequences were used to rate leukoaraiosis using the four-point Fazekas scale.[16] ICH volumes were calculated by outlining regions of interest on

Table 1 Demographic and imaging characteristics by race

	Black (n = 42)	White (n = 45)	*p* Value
Age, mean	63	73	<0.001*
Women (%)	24 (57)	23 (51)	0.668
Hypertension (%)	39 (93)	28 (62)	0.001*
Untreated hypertension (%)	23 (52)	10 (24)	0.007*
Diabetes mellitus (%)	10 (23)	6 (13)	0.271
CAD (%)	4 (9)	6 (15)	0.215
Hyperlipidemia (%)	8 (19)	10 (22)	0.795
Prior stroke (%)	4 (10)	8 (17)	0.356
Tobacco use (%)	15 (36)	10 (22)	0.236
Antiplatelet therapy (%)	8 (19)	14 (31)	0.225
Anticoagulation (%)	2 (5)	1 (2)	0.349
Heavy alcohol consumption (%)	10 (24)	5 (11)	0.117
One or more microbleeds (%)	31 (74)	19 (42)	0.005*
No. of microbleeds, median (interquartile range)	3 (0–10)	0 (0–2)	0.002*
ICH volume, mean cc (interquartile range)	20.0 (4.05–25.2)	24.9 (4.5–32.6)	0.346
Primary ICH lobar (%)	12 (29)	16 (36)	0.502
Moderate-severe leukoaraiosis (%)	29 (69)	13 (29)	<0.001*
Chronic hematomas (%)	13 (31)	7 (16)	0.088

*Significant.
CAD = coronary artery disease; ICH = intracerebral hemorrhage.

each slice using semiautomated image segmentation tools (Cheshire, Perceptive Informatics, Inc., Boulder, CO).

Statistical analyses. Differences in dichotomous variables between the black cohort and the white cohort were analyzed using χ^2 analysis or Fisher exact test. The Student *t* test or the Mann–Whitney *U* test was used to analyze differences in the mean or median of continuous variables between groups. Logistic regression analysis was performed to test the predictive value for microbleed occurrence (presence of 1 or more) employing the SPSS forced entry method. Risk factors that were significant on univariate analysis were included; age and hypertension were also forced into the model based on prior studies suggesting these items are significant risk factors.[17,18] A second analysis replaced history of hypertension with untreated hypertension. All statistical analyses were performed using the Statistical Package for the Social Sciences version 14.0 (SPSS, Chicago, IL).

RESULTS A total of 87 patients were included in this study (42 black, 45 white) out of 243 patients with a diagnosis of primary ICH seen by the stroke team during the study period. Patient demographic characteristics are shown in table 1. The black cohort was younger ($p < 0.001$), and had a greater rate of hypertension overall ($p = 0.001$) as well as untreated hypertension ($p = 0.007$) but not other vascular risk factors (table 1).

Table 1 also shows the imaging characteristics by race. Microbleeds were more prevalent in the black population, with 74% of black patients having one or more microbleeds compared to 42% of whites ($p = 0.005$) (table 1). Further, the overall microbleed burden was also greater in the black patients compared to the white patients: median number of microbleeds 3 (interquartile range 0–10) vs 0 (interquartile range 0–2) ($p = 0.002$).

The location of the primary ICH did not differ by race, with equal numbers of the black and white cohorts having their acute ICH in lobar regions (29% vs 36%, $p = 0.502$). Nor was there a difference in hematoma volumes by race (mean 20.0 mL for blacks, 24.9 for whites, $p = 0.346$). The black population tended to have a greater occurrence of chronic hematomas compared to the white population (31% vs 16%, $p = 0.088$) with a difference in the total number of chronic hematomas observed by group (23 vs 13, $p = 0.014$). Sixty-nine percent of blacks were found to have moderate-severe leukoaraiosis (table 1, figure 1), compared to only 29% of whites ($p < 0.001$).

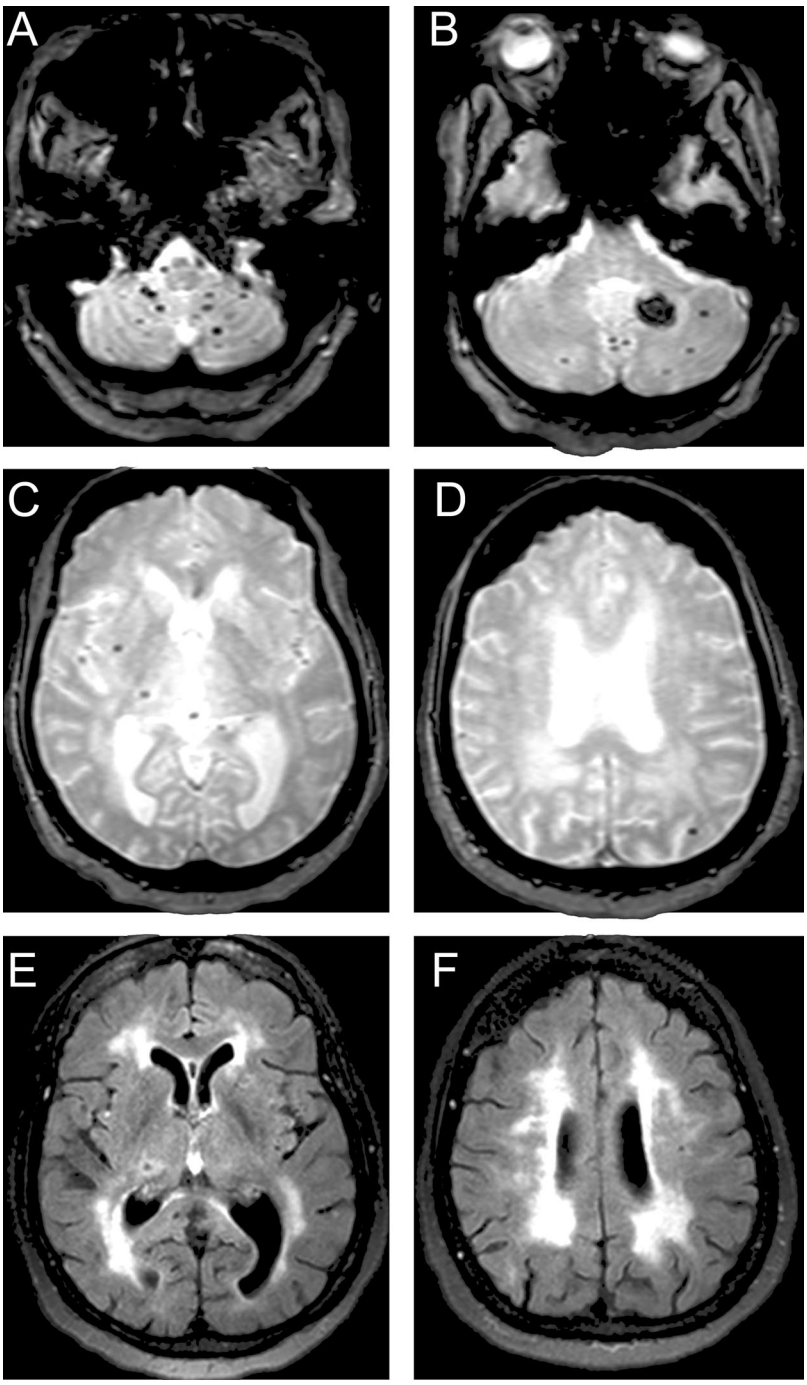
There was a notable difference in microbleed topography by race. While the white population had more lobar microbleeds (71% vs 54%, $p < 0.001$), the black population had more subcortical/deep (27% vs 18%, $p = 0.009$) and infratentorial microbleeds (19% vs 11%, $p = 0.009$). Of note, the black population also tended to have a greater frequency of microbleeds in multiple territories than the white population (38% vs 22%, $p = 0.106$). Figures 1 and 2 demonstrate case examples.

Table 2 provides the univariate analysis of risk factors for microbleeds. Neither age nor hypertension were significantly associated with microbleed presence; however, race and heavy alcohol consumption were. On logistic regression analysis (table 3), when adjusting for age and history of hypertension, both heavy alcohol use (OR 5.28, 95% CI 1.062–26.28, $p = 0.042$) and race (OR 3.308, 95% CI 1.144–9.571, $p = 0.027$) appeared as independent predictors of microbleeds. Similar results were found when substituting untreated hypertension for history of hypertension.

Imaging findings also differed for patients with and without microbleeds. Only 30% of microbleed negative patients had moderate to severe leukoaraiosis compared to 62% of microbleed positive patients ($p = 0.003$). Although there was no significant difference in ICH volumes for the acute hematomas between groups, microbleed positive patients had more chronic hematomas compared to patients without microbleeds (49 vs 37, $p < 0.001$).

DISCUSSION Several population-based studies have consistently demonstrated that primary ICH is

Figure 1 **Representative axial slices from GRE (A–D) and FLAIR (E–F) sequences from a 78-year-old black woman admitted with a presumed hypertensive left cerebellar hemorrhage**



GRE sequences also demonstrate a large number of microbleeds predominantly located within the posterior fossa, although a few scattered microbleeds are detected in lobar and deep supratentorial regions. FLAIR images demonstrate moderately severe small vessel white matter disease. GRE = gradient echo imaging; FLAIR = fluid-attenuated inversion recovery.

significantly more frequent in predominantly medically underserved populations, including black and Hispanic populations.[19-21] Our goal was to perform a detailed study of microbleed frequency and topography in an underserved black population with ICH.

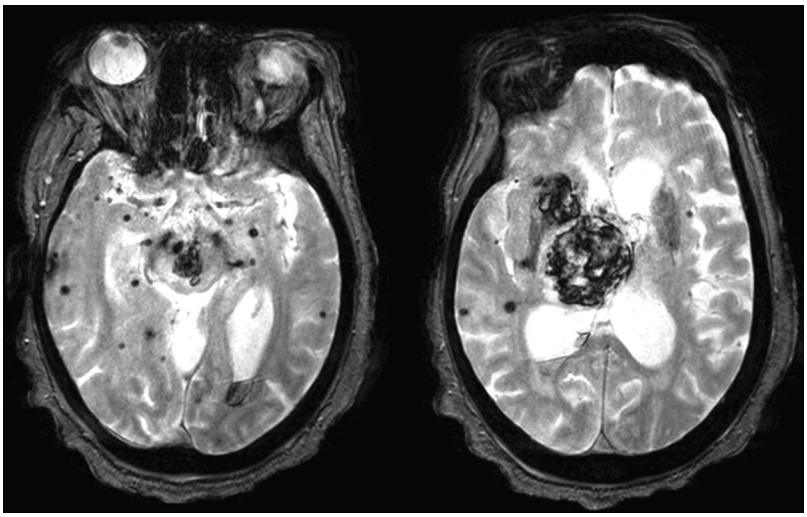
The current study suggests that significant racial differences exist in the frequency and topography of microbleeds in patients with primary ICH. The increased frequency of microbleeds in the black population likely reflects the underlying etiology and control (or lack thereof) of risk factors for hemorrhage. A history of hypertension as well as untreated hypertension were significantly more frequent in the black population compared to the white population. However, only pre-existing hypertension was identified, not hypertension diagnosed during hospitalization.

It is interesting to note that only race and heavy alcohol use, but not age or hypertension, were independent predictors of microbleeds on multivariate analysis. It is likely that hypertension was not significant due to the extremely high prevalence of this risk factor in the black population. It is therefore reasonable to postulate that the degree of uncontrolled hypertension was not measured precisely enough to capture its effects, and that black race was actually a better marker of severe hypertension. The alternative possibility is that black race is associated with microbleeds through a blood pressure–independent mechanism. Of note, leukoaraiosis, which may serve as an important biomarker of uncontrolled vascular risk factors such as hypertension, was significantly more frequent both in the black population as a whole compared to white subjects, but also in the microbleed positive group compared to the microbleed negative group.

Similarly, in patients with acute ischemic stroke, a recent study of the prevalence of microbleeds revealed that blacks were more likely to have two or more microbleeds than whites, while the overall prevalence of at least one microbleed did not vary by race. This study also found that hypertension was the only independent predictor of microbleeds in patients with acute ischemic stroke.[13] The increased frequency of multiple microbleeds in black patients with both ICH and acute ischemic stroke suggests that microbleeds may be an important surrogate marker of disease control in this population.

The results of the current study suggest that the burden of vasculopathic disease in black patients may be even greater than previously believed compared with white patients and can be well quantified on MR imaging. Although this increased disease burden is most likely due to the increased incidence of hypertension in the black population, the relative contribution of other risk factors is poorly understood. Despite the relatively small sample size, heavy alcohol use did emerge as a significant predictor of mi-

Figure 2 Representative axial gradient echo images from a 78-year-old black woman with a history of hypertension only with a right thalamic hemorrhage and microbleeds located in both lobar and deep locations



crobleeds in multivariate analysis. This finding is consistent with prior studies that found that heavy alcohol consumption may be an important risk factor for primary ICH.[2,22,23] Of note, it is not possible in this current study to delineate the relative contributions of control of other risk factors or SES.

An intriguing finding from this study is the overall topography of microbleeds in the two different populations. The black cohort not only had a greater overall burden of microbleeds in the subcortical/deep territories as is expected due to the higher frequency of hypertension, but also had a greater occurrence of microbleeds in multiple locations including both infratentorial and lobar territories. This increased frequency in multiple regions is more difficult to explain by hypertension alone, and potentially points to additional previously unidentified underlying etiologies (e.g., does race contribute to genetic risk for amyloid angiopathy?).

Table 2 Risk factors and univariate predictors of presence of one or more microbleeds

	No microbleeds (n = 37)	One or more microbleeds (n = 50)	*p* Value
Age, mean	70	67	0.212
Women, %	57	52	0.660
Black race, n (%)	11 (30)	31 (62)	0.003*
Hypertension, %	70	82	0.199
Untreated hypertension, %	30	44	0.175
Diabetes mellitus, %	19	18	0.913
CAD, %	16	6	0.122
Hyperlipidemia, %	24	18	0.472
Prior stroke, %	8	18	0.188
Tobacco use, %	19	36	0.082
Antiplatelet therapy, %	27	24	0.748
Anticoagulation, %	0	8	0.078
Alcohol use, %	5	26	0.012*

*Significant.
CAD = coronary artery disease.

Table 3 Logistic regression model of risk factors predicting one or more microbleeds

	OR	95% CI	*p* Value
Race	3.308	1.144–9.571	0.027*
Alcohol	5.284	1.062–26.280	0.042*
Age	0.997	0.957–1.038	0.878
Hypertension	1.092	0.354–2.266	0.878

*Significant.

While the pathophysiology of microbleed formation has yet to be fully explained, a compelling story is emerging regarding the prognostic role of microbleeds and primary intracerebral hemorrhage. The relevance of microbleeds in patients with cerebral amyloid angiopathy has been extensively studied. In patients with probable CAA and lobar hemorrhage, the number of microbleeds predicts the risk of future symptomatic ICH,[24] and new microbleeds on repeat MR imaging predict increased risk of future symptomatic ICH.[5] Moreover, microbleed burden and rate of accumulation predict cognitive decline and poor neurologic/functional outcome,[24] suggesting that microbleeds have the potential to serve as useful surrogate markers of long-term prognostic outcome. However, these prior studies have included primarily a middle-class white population with amyloid angiopathy rather than hypertensive small vessel disease, and therefore little is known about microbleeds and ICH in both black patients and patients with poorly controlled risk factors.

Limitations of this pilot study include its retrospective design, which made it not possible to extrapolate reliable information regarding SES. SES and race may be confounding factors for hemorrhage and microbleed risk. For example, the primarily medically underserved black cohort from one hospital may have had poor risk factor (hypertension) control due to lack of health care access.

However, there were insufficient numbers of racially balanced patients within a single hospital to allow an analysis by hospital, and even this would not guarantee SES parity. For these reasons, a prospective study evaluating a larger number of patients across various SESs will be important to answer this question. In addition, the logistic regression model used more independent variables then may be recommended for the sample size; this increases the likelihood that some relationships identified are due to chance. It is also important to note that the models have not yet been validated in an independent cohort. Finally, data were collected on two MRI scanners with different field strengths, introducing a possible bias for greater microbleed detection on the stronger magnet. However, as noted previously a retrospective blinded comparison of 31 patients with GRE sequences performed on both 1.5 T and 3.0 T scanners found that microbleed detection is equivalent on the two scanners.

Our findings raise a number of important questions. If the increased frequency of hemorrhage in black patients is due primarily to hypertension, why are microbleeds located in lobar regions in many of these patients with deep hemorrhages? Are there additional contributing risk factors? Why are microbleeds clustered in specific regions in some patients but not others? And perhaps most importantly, do the presence, lesion burden, and rate of accumulation over time of new microbleeds provide important prognostic information that could be used to optimize patient care? Further long-term prospective clinical and imaging natural history studies are needed to elucidate the underlying pathophysiology of ICH and microbleeds.

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From the AAN History Library Collection
Osler's *The Cerebral Palsies of Children* (1889)

Position of child in walking.

William Osler's monograph, *The Cerebral Palsies of Children* (1889), was a slightly updated compilation of a series of lectures he presented in 1888, based on clinical and pathological studies he conducted at the Philadelphia Orthopedic Hospital and Infirmary for Nervous Diseases. Osler's monograph was one of the first critical analyses of cerebral palsy and childhood stroke; it continues to be recognized and frequently cited for its contributions to classifying the forms of cerebral palsy and childhood stroke, and for its elaborations of the clinical, etiological, and pathological differences between the different forms, specifically infantile hemiplegia, bilateral spastic hemiplegia (diplegia), and spastic paraplegia. His clinical and pathological material was based on his own experience in Philadelphia, that of his close colleagues Silas Weir Mitchell and Wharton Sinkler, and those of Dr. Kerlin, Superintendent of the Philadelphia Institute for Feeble-minded Children at Elwyn. The figure, from Osler's monograph, shows the scissoring gait of a child with cerebral palsy.

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1. Osler W. The Cerebral Palsies of Children: A Clinical Study from the Infirmary for Nervous Diseases, Philadelphia. London: H.K. Lewis [and separately Philadelphia: P. Blakiston, Son & Co.], 1889

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